Targeting CD73 for Treatment of Triple Negative Breast Cancer

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Awarded: $900,000.00

Grant Mechanism: Investigator Initiated Research

Public Abstract:
Triple negative breast cancer accounts for 15-20% of all breast cancers. Most importantly, patients with triple negative breast cancer have a worse chance of survival compared to other forms of breast cancer. Another important feature of triple negative breast cancer is that it is associated with an increased risk of metastasis to vital organs. Indeed, approximately 70% of first distant recurrence arises in the lungs or brain. Women with triple negative breast cancer are treated with toxic chemotherapeutic drugs. Unfortunately, only a minority of patients respond to treatment for yet unknown reasons. Thus, the risk of metastasis to vital organs and the resistance to standard chemotherapy are the two major obstacles in the treatment of triple negative breast cancer. We have recently found that expression of a protein called CD73 on breast cancer cells is associated with an increased resistance to chemotherapy. We observed that patients who have high levels of CD73 in their tumor have a lower chance of responding to treatment compared to patients with low levels of CD73. CD73 is protein that we recently identified as playing an important role in triple negative breast cancer. Our studies showed that CD73 suppresses the immune system, thereby allowing breast tumors to progress unimpeded. We also demonstrated that expression of CD73 on breast tumor cells enhances their potential to form lung metastasis. We now propose a new role for CD73. We hypothesize that CD73 promotes chemo resistance and that anti-CD73 therapies can reverse this resistance. What we have learned from our previous studies is that anti-CD73 therapy enhances the ability of immune cells to kill tumor cells. We also propose that combining anti-CD73 therapy with other forms of immune-activating therapies with provoke strong anti-tumor activity. We will thus investigate the anti-tumor activity of combining anti-CD73 therapy with monoclonal antibodies currently approved or in clinical trials for cancer treatment, namely anti-CTLA-4, anti-PD-1 and anti-CD137 mAb. Finally, we will further study the mechanisms by which CD73 promotes breast cancer metastasis. In conclusion, our approach could represent a novel form of treatment against metastatic triple negative breast cancer. Our approach could also be used as adjuvant therapy in patients at high risk for recurrence. This project could provide the basis for the development of new targeted therapies against triple negative breast cancer and against breast cancer in general.